GEORGIA INSTITUTE OF TECHNOLOGY — OFFICE OF CONTRACT ADMINISTRATION

PROJECT ADMINISTRATION DATA SHEET

[X] ORIGINAL [ ] REVISION NO. _____

Project No. E-25-687 (R5823-0A1) GTRC/~~GIT~~ DATE 7 / 23 / 86

Project Director: D. P. Giddens School/~~Lab~~ ME

Sponsor: National Science Foundation

Type Agreement: Grant No. MSM-8312391

Award Period: From 6/1/84 To 5/31/87 (Performance) 8/31/87 (Reports)

Sponsor Amount:	This Change	Total to Date
Estimated:	$	$ 73,719.28
Funded:	$	$ 73,719.28

Cost Sharing Amount: $ _____ Cost Sharing No: _____

Title: Pulsatic Flow and the Susceptibility of Arteries to Atherosclerosis

ADMINISTRATIVE DATA — OCA Contact John B. Schonk X-4820

1) Sponsor Technical Contact:

Stephen C. Traugott
National Science Foundation
ENG/MSM
Washington, DC 20550

202/357-9542

2) Sponsor Admin/Contractual Matters:

H.D. Wolff, III
National Science Foundation
DGC/ENG
Washington, DC 20550

202/357-9602

Defense Priority Rating: N/A Military Security Classification: N/A

(or) Company/Industrial Proprietary: N/A

RESTRICTIONS

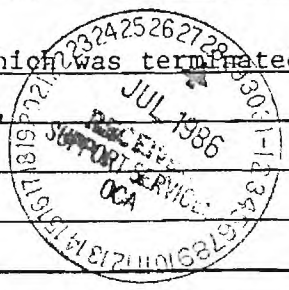
See Attached NSF Supplemental Information Sheet for Additional Requirements.

Travel: Foreign travel must have prior approval — Contact OCA in each case. Domestic travel requires sponsor approval where total will exceed greater of $500 or 125% of approved proposal budget category.

Equipment: Title vests with GIT

COMMENTS:

This project account is set up to be the continuation of E-16-679 which was terminated because the PI transferred from the School of Aerospace Engineering.



COPIES TO: SPONSOR'S I. D. NO. _____

Project Director	Procurement/GTRI Supply Services	GTRC
Research Administrative Network	Research Security Services	Library
Research Property Management	Reports Coordinator (OCA)	Project File
Accounting	Research Communications (2)	Other A. Jones

GEORGIA INSTITUTE OF TECHNOLOGY
OFFICE OF CONTRACT ADMINISTRATION

NOTICE OF PROJECT CLOSEOUT

Closeout Notice Date 02/01/90
Original Closeout Started *********

Project No. E-25-687 Center No. R5823-0A1

Project Director GIDDENS D School/Lab ME

Sponsor NATL SCIENCE FOUNDATION/GENERAL

Contract/Grant No. MSM-8312391 Contract Entity GTRC

Prime Contract No. _____

Title PULSATILE FLOW AND THE SUSCEPTIBILITY OF ARTERIES TO AN~~THEROSCLEROSIS~~ Atherosclerosis

Effective Completion Date 880531 (Performance) 880831 (Reports)

Closeout Actions Required:	Y/N	Date Submitted
Final Invoice or Copy of Final Invoice	N	_____
Final Report of Inventions and/or Subcontracts	N	_____
Government Property Inventory & Related Certificate	N	_____
Classified Material Certificate	N	_____
Release and Assignment	N	_____
Other _____	N	_____

Subproject Under Main Project No. _____

Continues Project No. _____

Distribution Required:

Project Director	Y
Administrative Network Representative	Y
GTRI Accounting/Grants and Contracts	Y
Procurement/Supply Services	Y
Research Property Managment	Y
Research Security Services	N
Reports Coordinator (OCA)	Y
GTRC	Y
Project File	Y
OCA/CSD	N
Other _____	N
_____	N

E-25-687

GEORGIA TECH RESEARCH CORPORATION

GEORGIA INSTITUTE OF TECHNOLOGY
ATLANTA, GEORGIA 30332-0420

Telex 542507 GTRCOCAATL
Fax (404) 894-3120

Phone (404) 894-4817

Refer to: RDF/02.107.000.87.074

December 31, 1986

National Science Foundation
1800 G Street, N.W.
Washington, DC 20550

Attention: Stephen C. Traugott
Fluid Mechanics and Hydraulics Program Mechanics,
Structures and Materials Engineering

Subject: Grant No. MSM-8312391; Request for Incremental Funding for Continuing Grant entitled, "Pulsatile Flow and the Susceptibility of Arteries to Atherosclerosis"

Dear Dr. Traugott:

In accordance with NSF Grant Policies, the GTRC is pleased to submit the Annual Progress Report and Request for Continued Support on the subject research project.

We believe that the enclosed material will provide you with all the necessary information. However, if additional information is required, please contact Dr. Giddens at (404) 894-3781 concerning the technical program. Contractual matters should be referred to the undersigned at (404) 894-4817.

We appreciate the opportunity of submitting this request and look forward to the possibility of continuing our work with you on this project.

Cordially,

R. Dennis Farmer
Contracting Officer

RDF/sdm

Addressee: In triplicate
Enclosures: Progress Report - in triplicate
Proposal Budget - in triplicate

APPENDIX VII

NATIONAL SCIENCE FOUNDATION
Washington, D.C. 20550

FINAL PROJECT REPORT
NSF FORM 98A

PLEASE READ INSTRUCTIONS ON REVERSE BEFORE COMPLETING

PART I–PROJECT IDENTIFICATION INFORMATION

1. Institution and Address	2. NSF Program	3. NSF Award Number
Georgia Tech Research Corporation Georgia Institute of Technology Atlanta, GA 30332	Fluid Mechanics & Hydraulics	MEA-8312391
	4. Award Period From 6/1/84 To 11/30/87	5. Cumulative Award Amount $385,031

6. Project Title

Pulsatile Flow and the Susceptibility of Arteries to Atherosclerosis

PART II–SUMMARY OF COMPLETED PROJECT *(FOR PUBLIC USE)*

SUMMARY OF PROGRESS

The overall goals of this research are to advance basic knowledge in unsteady fluid dynamics and to identify specific fluid mechanical mechanisms which contribute as causative factors to the initiation and progression of atherosclerosis. The Georgia Tech program is a companion study to a project underway in the Departments of Surgery and Pathology at the University of Chicago Medical School under the direction of Drs. C.K. Zarins and S. Glagov. Fluid dynamical studies are carried out at Georgia Tech and biological investigations are performed at the University of Chicago.

Since our progress report on work performed during 1985, in which we summarized findings relating near wall flow behavior with the localization of atherosclerotic lesions, we have concentrated at Georgia Tech on three primary areas: (i) the decomposition and characterization of velocity disturbances in a transitional pulsatile flow; (ii) computational methods for describing hemodynamic behavior; and (iii) development of transparent compliant models of the carotid artery. In the area of velocity disturbance analysis our previous studies demonstrated that the "standard" method of determining an underlying waveform in pulsatile flow by forming an ensemble average does not cleanly separate random from repeatable flow structures in a transitional pulsatile flow. Thus, estimates of random stresses are contaminated by coherent fluctuations even when using the triple decomposition approach. We have pursued this work and developed a new method based upon adaptive filtering in the frequency domain which appears to be successful in cleanly decomposing the velocity into random and coherent components. This may have implication to the theoretical concept of triple decomposition favored by turbulence investigators in that improved data analysis may allow better modeling of turbulence phenomena.

(continued on next page)

PART III–TECHNICAL INFORMATION *(FOR PROGRAM MANAGEMENT USES)*

ITEM *(Check appropriate blocks)*	NONE	ATTACHED	PREVIOUSLY FURNISHED	TO BE FURNISHED SEPARATELY TO PROGRAM	
				Check (✓)	Approx. Date
a. Abstracts of Theses			X		
b. Publication Citations		X	X		
c. Data on Scientific Collaborators			X		
d. Information on Inventions	X				
e. Technical Description of Project and Results		X	X		
f. Other *(specify)*					

2. Principal Investigator/Project Director Name *(Typed)*	3. Principal Investigator/Project Director Signature	4. Date
Don P. Giddens		12/29/88

NSF Form 98A (3-83) Supersedes All Previous Editions

Form Approved OMB No. 3145-0058

SUMMARY OF PROGRESS (continued)

Because of the unsteady and three dimensional nature of many blood flow situations, we have begun work on two approaches in computational fluid dynamics: a steady three-dimensional finite difference method which employs a fast algebraic grid generation method for internal boundaries based upon geometric projection of cross-sections and which utilizes primary variables in the flow field solution; and an unsteady, low Mach number compressible approach for approximating certain types of incompressible flow behavior. Both methods are being applied to internal flows of interest in arterial fluid mechanics including flow in curved tubes, flow through constrictions and aneurysms, and flows in bifurcations. The steady, three dimensional code has successfully calculated separated flows and secondary flows, and we are presently investigating a flow field which contains both features. The compressible unsteady code is two dimensional at present, and we have employed it to compute separated flow through a mild constriction for an asymptotically steady state case. This is now being extended to pulsatile flow through a mild constriction.

In an effort to continue the evolution of modeling arterial flows realistically, we have developed a technique to construct transparent compliant models of the human carotid bifurcation. This will allow us to model arterial wall motion which was not possible with the rigid plexiglass models employed heretofore in our work. The transparent material allows use of laser Doppler anemometry and permits us to achieve a good index of refraction match between the model and the working fluid using a fluid (a simple glycerine/ water solution) which is neither unpleasant in odor, combustible nor expensive. We will use these models to investigate the effects of wall motion on flow behavior in the immediate vicinity of the vessel walls.

Papers Published in 1986 from NSF Support

N. Talukder, J.T. Fulenwider, R.F. Mabon, D.P. Giddens, "Poststenotic FLow Disturbance in the Dog Aorta as Measured with Pulsed Doppler Ultrasound," Journal of Biomechanical Engineering, Vol. 108, pp. 259-265, 1986.

R.I. Kitney, H. Talhami and D.P. Giddens, "The Analysis of Blood Velocity Measurements by Autoregressive Modelling," Journal of Theoretical Biology, Vol. 120, pp. 419-442, 1986.

R.I. Kitney and D.P. Giddens, "Linear Estimation of Blood Flow Waveforms Measured by Doppler Ultrasound," MEDINFO 86, Proceedings of the Fifth Conference on Medical Informatics, Washington, October 26-30, 1986, Pt.2, pp. 672-677.

Manuscripts Submitted in 1986 from NSF Support

D.N. Ku and D.P. Giddens, "Laser Doppler Anemometer Measurements of Pulsatile Flow in a Model Carotid Bifurcation" Accepted for publication in Journal of Biomechanics.

B.B. Lieber and D.P. Giddens, "Apparent Stresses in Disturbed Pulsatile Flow" Submitted to Journal of Biomechanics.

B.B. Lieber and D.P. Giddens, "Autoregressive Spectral Estimation in Transitional Pulsatile Flow" Submitted to Physics of Fluids.

B.B. Lieber, D.P. Giddens, R.I. Kitney and H. Talhami, "The Discrimination Between Coherent and Random Apparent Stresses in Transitional Pulsatile Flow" Submitted for presentation at 1987 Fluid Engineering Spring Conference.

Papers Presented at Scientific Meetings in 1986 from NSF Support

B.B. Lieber and D.P. Giddens, "Contamination of Reynolds Stress Determinations in Pulsatile Disturbed Flows," Fifth International Conference on Mechanics in Medicine and Biology, Bologna, Italy.

D.P. Giddens, "Unsteady Wall Shear Phenomena and Atherosclerosis" Scientific Symposium at the Occasion of the 600th Anniversary of the University of Heidelberg (invited)

B.B. Lieber and D.P. Giddens, "Estimation of Reynolds Stresses in Pulsatile Disturbed Flows" 39th Annual Conference on Engineering in Medicine and Biology, Baltimore.

B.B. Lieber, D.P. Giddens, C.K. Zarins and S.G. Glagov, "Pulsatile Near Wall Studies Distal to Coarctations," ASME Winter Annual Meeting, Anaheim.

E-25-687

NATIONAL SCIENCE FOUNDATION
Washington, D.C. 20550

FINAL PROJECT REPORT
NSF FORM 98A

PLEASE READ INSTRUCTIONS ON REVERSE BEFORE COMPLETING

PART I—PROJECT IDENTIFICATION INFORMATION

1. Institution and Address	2. NSF Program	3. NSF Award Number
Georgia Institute of Technology Atlanta, GA 30332	Fluid Mechanics	MSM-8312391
	4. Award Period From 6/1/84 To 5/30/88	5. Cumulative Award Amount $373,915.00

6. Project Title
Pulsatile Flow and the Susceptibility of Arteries to Atherosclerosis

PART II—SUMMARY OF COMPLETED PROJECT *(FOR PUBLIC USE)*

This research was an investigation of pulsatile fluid dynamics in artery models with the objective of determining whether specific types of fluid flow behavior are associated with the localization of atherosclerotic plaques. The research took the approach that correlations between flow field variables measured in laboratory models and biological variables measured in animal and human arteries should uncover those fluid dynamic factors which participate in the genesis of arterial disease. The fluid dynamics research was performed under this grant, and the biological studies were carried out at The University of Chicago School of Medicine under separate funding. Several key findings resulted. (i) Atherosclerotic plaques in the human carotid artery localize in regions where the mean wall shear stress is low (below approximately 10 dynes/sq cm) or oscillatory in direction; regions where the wall shear is higher and unidirectional are spared from early atherosclerosis. (ii) Femoral arteries in the cynomolgus monkey react to a chronic increase in wall shear by remodeling their structure until the vessel diameter reaches a value that results in a mean wall shear stress of approximately 15 dynes/sq cm. (iii) Thickening of the intima, the layer of the artery between the endothelial cells and the media, in the region downstream of aortic stenoses in cynomolgus monkeys correlates well with the reciprocal of the maximum absolute value of wall shear stress during the pulsatile cycle. (iv) Turbulence and high wall shear stresses are not atherogenic factors. These studies have lead to the hypotheses that (a) intimal thickening is a natural response of the artery wall to low or oscillatory wall shear and (b) intimal thickening may result in atherosclerotic plaque if blood contains sufficient atherogenic macromolecules which have long particle residence times at these susceptible regions. Current research is focused upon testing these hypotheses.

PART III—TECHNICAL INFORMATION *(FOR PROGRAM MANAGEMENT USES)*

1. ITEM *(Check appropriate blocks)*	NONE	ATTACHED	PREVIOUSLY FURNISHED	TO BE FURNISHED SEPARATELY TO PROGRAM	
				Check (✓)	Approx. Date
a. Abstracts of Theses		X			
b. Publication Citations		X			
c. Data on Scientific Collaborators		X			
d. Information on Inventions	X				
e. Technical Description of Project and Results		X			
f. Other *(specify)*					

2. Principal Investigator/Project Director Name *(Typed)*	3. Principal Investigator/Project Director Signature	4. Date

Form Approved OMB No. 3145-0058

RESULTS FROM PRIOR NSF SUPPORT

The PI has had a series of grants from NSF. The following is the most recent: MSM-8312391, *Pulsatile Flow and the Susceptibility of Arteries to Atherosclerosis*, $373,915, July 1, 1984 through May 31, 1988.

Summary

This summary will cover results from approximately the past five years.

Collaborative research between the Principal Investigator and biomedical investigators at The University of Chicago has resulted in significant contributions in the field of biofluid dynamics and vascular disease. These results are summarized below.

1. **Atherosclerotic plaques in the human carotid artery localize in regions where the mean wall shear stress is low (below approximately 10 dynes/cm^2) or oscillatory in direction. Regions where the wall shear is relatively high and unidirectional are spared from atherosclerosis.**

Before our paper in Circulation Research (1) was published, the scientific community was divided in opinion as to whether low wall shear or high wall shear is the fluid dynamic factor associated with plaque localization. This paper, which correlated steady flow velocity measurements in a model of the human carotid bifurcation with measurements of intimal thickening obtained from human subjects, was the first to demonstrate that plaque localization is associated with low fluid dynamic wall shear. A second paper (2) examined the effects of pulsatility on the flow field and, although certain fluid dynamic features are different than for steady flow, the basic finding of Reference (1) was sustained, provided that mean wall shear was used in the correlations. Reference (2) did introduce the concept of wall shear oscillations perhaps being an associative factor.

These studies also discussed the possible role of long residence time of atherogenic

particles near cellular sites of macromolecular uptake. This suggestion has not yet been explored.

2. **Femoral arteries in the cynomolgus monkey react to a chronic increase in blood flow rate by remodeling their structure until the vessel diameter reaches a value that results in a mean wall shear stress of approximately 15 dynes/cm^2 (3).**

We performed a series of studies in which a fistula was installed between the femoral artery and vein in one hind limb of cynomolgus monkeys while the contralateral femoral artery served as a control. Flow in the artery on the fistula side increased by an order of magnitude as a consequence of the low pressure in the vein. After six months, the diameters of the femoral arteries were such that the average wall shear stress was approximately 15 dynes/cm^2, regardless of the flow rate. These data are consistent with studies in the literature in other animal species (4,5). Languille (6) presents data which suggest that these arterial modifications are mediated by the response of endothelial cells to the changes in flow rate, presumably (though not proven) by reacting to fluid dynamic wall shear stress.

We have combined our studies of artery adaptation in response to changes in flow (and those of other investigators, as well) with the results of our investigations of atherogenesis in the human carotid bifurcation (1,2) to hypothesize that (i) intimal thickening is a natural arterial response to low or oscillatory wall shear and (ii) intimal thickening may result in atherosclerotic plaque if blood contains atherogenic macromolecules which have long particle residence time in these susceptible regions. Much of our current research is directed toward testing these hypotheses.

3. **Intimal thickening in the region downstream of aortic stenoses in cynomolgus monkeys correlates well with the reciprocal of the maximum absolute value of wall shear stress during the pulsatile cycle.**

The implication of this finding is that intimal thickening does not occur unless the local

value of wall shear is continually low (3). Large excusions in shear, even though the time average is low, result in regions of sparing from intimal thickening.

4. **Turbulence and high wall shear stresses are not atherogenic factors.**

This conclusion results from several studies we performed in which neither high wall shear stress nor turbulence correlated with the localization of early atherosclerotic lesions. Our studies disproved the concept that atherosclerosis is initiated by damage to the artery wall induced by large shear stress.

Thus, our previous research has identified a small set of fluid dynamic factors (low wall shear, wall shear oscillations and long particle residence time) which correlate with pathological behavior of the artery wall. Primary flow field features, such as separation and recirculation, appear to provide a micro- environment conducive to artery wall pathology. However, mechanisms by which the fluid-surface interaction occurs are not known. Two schools of thought are (i) endothelial cells require sufficiently high levels of fluid dynamic wall shear stress to maintain physiological homeostasis and (ii) enhanced mass transport of macromolecules occurs in regions of long particle residence time. Further advances will require improved knowledge of microscopic fluid dynamics in the neighborhood of the vessel surface. It is in this direction that our biological fluid dynamic studies are proceeding.

References

[1] Zarins, C.K., Giddens, D.P., Bharadvaj, B.K., Sottiurai, V.S., Mabon, R.F., and Glagov,S., *Carotid Bifurcation Atherosclerosis: Quantitative Correlation of Plaque Localization with Flow Velocity Profiles and Wall Shear Stress,* **Circulation Research**, Vol. 53, pp. 502-514, 1983.

[2] Ku, D.N., Giddens, D.P., Zarins, C.K., and Glagov, S., *Pulsatile Flow and Atherosclerosis in the Human Carotid Bifurcation: Positive Correlation between Plaque Location and Low and Oscillating Shear Stress,"* **Arteriosclerosis**, Vol. 5, pp. 293-302, 1985.

[3] Zarins, C.K., Zatina, M.A., Giddens, D.P., Ku, D.N., and Glagov, S., *Shear Stress Regulation of Artery Lumen Diameter in Experimental Atherogenesis,* **Journal of Vascular Surgery**, Vol. 5, pp. 413-420, 1987.

[4] Kamiya, A. and Togawa, T., *Adaptive Regulation of Wall Shear Stress to Flow Change in the Canine Carotid Artery,* **American Journal of Physiology**, Vol. 239, pp. 414-421, 1980.

[5] Guyton, J.R., Hartley, C.J., *Flow Restriction of One Carotid Artery in Juvenile Rats Inhibits Growth of Arterial Diameter,* **Am J. Physiol**, Vol. 248, pp. H540-H546, 1985.

[6] Languille, B.L. and O'Donnell, F., *Reductions in Arterial Diameter Produced by Chronic Decreases in Blood Flow are Endothelium-Dependent,* **Science**, Vol. 231, pp.405-407, 1986.

Publications resulting from sponsored NSF grants: (last five years)

[1] Lieber, B.B., and Giddens, D.P., *Poststenotic Core Flow Behavior in Pulsatile Flow and its Effects on Wall Shear Stress*, Submitted to **Journal of Biomechanics** for publication, 1989. (MEA-83-12391)

[2] Zarins, C.K., Glagov, S. and Giddens, D.P., *What do we find in Human Atherosclerosis that Provides Insight into the Hemodynamic Factors in Atherogenesis?*, Chapter 21, pp 317-332, **Pathobiology of the Human Atherosclerotic Plaque**, Springer-Verlag New York, Editors: Glagov, S., Newman, III, W.P., and Schaffer, S.A., 1989. (CME 7921551)

[3] Lieber, B.B., Giddens, D.P., Kitney, R.I., and Talhami, H., *On the Discrimination Between Band-Limited Coherent and Random Apparent Stresses in Transitional Pulsatile Flow*, **Journal of Biomechanical Engineering**, Vol. 111, pp. 42-46, February 1989. MEA-83-12391)

[4] Giddens, D.P., and Nerem, R.M., *Challenging Computational Problems in Cardiovascular Fluid Mechanics*, **Computational Methods in Bioengineering - BED**, Vol. 9 (Book No. G00458, Editors: Spilker, R.L. and Simon, B.R., pp. 21-28, 1989. (MEA-8312391)

{5} Ku, D.N. and Giddens, D.P., *Laser Doppler Anemometer Measurements of Pulsatile Flow in a Model Carotid Bifurcation*, **Journal of Biomechanics**, Vol. 20, No. 4, pp. 407-421, 1987.

[6] Lieber, B.B., and Giddens, D.P., *Apparent Stresses in Disturbed Pulsatile Flow*, **Journal of Biomechanics**, Vol. 21, No. 4, pp. 287-298, 1988.

[7] Giddens, D.P. and Ku, D.N., *A Note on the Relationship Between Input Flow Waveform and Wall Shear Rate in Pulsatile, Separating Flows*, **Journal of Biomechanical Engineering**, Technical Brief, Vol. 109, pp. 175-176, May 1987.

[8] Giddens, D.P., and Ku, D.N., *A Note on the Relationship Between Input Flow Waveform and Wall Shear Rate in Pulsatile, Separating Flows*, **Journal of Biomechanical Engineering**, Technical Brief, Vol. 109, pp. 175-176, 1987. (MEA-8312391)

[9] Zarins, C.K., Zatina, M.A., Giddens, D.P., Ku, D.N., and Glagov, S., *Shear Stress Regulation of Artery Lumen Diameter in Experimental Atherogenesis*, **Journal of Vascular Surgery**, Vol. 5, pp. 413-420, 1987.

[10] Talukder, N., Fulenwider, J.T., Mabon, R.F., and Giddens, D.P., *Poststenotic Flow Disturbance in the Dog Aorta as Measured with Pulsed Doppler Ultrasound*, **Journal of Biomechanical Engineering**, Vol. 108, pp. 259-265, 1986.

[11] Kitney, R.I., Talhami, H., and Giddens, D.P., *The Analysis of Blood Velocity Measurements by Autoregressive Modelling*, **Journal of Theoretical Biology**, Vol. 120, pp. 419-442, 1986.

[12] Kitney, R.I. and Giddens, D.P., *Linear Estimation of Blood Flow Waveforms Measured by Doppler Ultrasound*, **MEDINFO 86**, Proceedings of the Fifth Conference on Medical Informatics, Washington, October 26-30, 1986, Pt. 2, pp. 672-677.

[13] Ku, D.N., Giddens, D.N., Zarins, C.K., and Glagov, S., *Pulsatile Flow and Atherosclerosis in the Human Carotid Bifurcation: Positive Correlation between Plaque Location and Low and Oscillating Shear Stress*, **Arteriosclerosis**, Vol. 5, pp. 293-302, 1985. (CME-7921551)

[14] Ku, D.N., Giddens, D.P., Phillips, D.J., and Strandness, Jr., D.E., *Hemodynamics of the Normal Human Carotid Bifurcation: In Vitro and In Vivo Studies*, **Ultrasound in Med. & Biol.**, Vol. 11, No. 1, pp. 13-26, 1985.

BIOGRAPHICAL SKETCH

Give the following information for all professional personnel contributing to the training program, beginning with the Program Director. Photocopy this page for each person.
(DO NOT EXCEED 2 PAGES ON ANY INDIVIDUAL)

NAME (Last, first, middle initial)	TITLE	BIRTH DATE (Mo., Day, Yr.)
Zarins, Christopher K.	Professor of Surgery Chief, Sect. of Vasc. Surg.	12/2/43

EDUCATION *(Begin with baccalaureate or other initial professional education and include postdoctoral training)*

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
Lehigh University, Bethlehem, PA	B.A.	1964	Biology
Johns Hopkins University Sch. of Medicine	M.D.	1968	Medicine
University of Michigan Hosp., Ann Arbor, MI	Intern/Resid.	1968-74	Surgery

HONORS: Phi Eta Sigma
Omicron Delta Kappa
Phi Beta Kappa
Resident Research Award, Association for Academic Surgery

MAJOR RESEARCH/PROFESSIONAL INTEREST: Pathogenesis of vascular disease, in particular atherosclerosis and the complications of vascular surgery and the biology of vascular compensation for disease and alterations in flow.

RESEARCH AND TRAINING SUPPORT *(See Instructions)*

SCOR Atherosclerosis Project B2: 12/1/86 - 11/30/91 (National Institutes of Health)
Total funding: $1,197,105 -- Grant No.: HL 15062-17/B-2 SCOR
National Science Foundation: 1/1/85 - 10/30/89
Total funding: $349,000 -- Grant No.: MSM-8416361
National Institutes of Health: 7/1/88 - 6/30/93
Total funding: $775,384 -- Grant No.: 1 RO2 HL 41267-01

RESEARCH AND PROFESSIONAL EXPERIENCE. List in reverse chronological order previous employment and experience. List in reverse chronological order all publications, or most representative if the 2 page limit on the sketch presents a problem.

1983 - present	Editor, Journal of Surgical Research
1982 - present	Professor of Surgery, University of Chicago
1979 - 1982	Associate Professor of Surgery, University of Chicago
1978 - present	Chief, Vascular Surgery, University of Chicago
1978 - 1985	Director, Vascular Laboratory, University of Chicago
1977 - 1983	Assistant and Associate Editor, Journal of Surgical Research
1976 - 1979	Assistant Professor of Surgery, University of Chicago
1974 - 1976	Research Director, Trauma Research Unit, Naval Regional Medical, San Diego, CA
1973 - 1974	Chief Resident in Surgery, University of Michigan, Ann Arbor, MI
1971 - 1972	Research Fellowship, Johns Hopkins University
1969 - 1973	General Surgical Residency, University of Michigan, Ann Arbor, MI
1968 - 1969	Surgical Internship, University of Michigan, Ann Arbor, MI

Publications:

1) Differential enlargement of artery segments in response to enlarging atherosclerotic plaques. C.K. Zarins, E. Weisenberg, G. Kolettis, R. Stankunavicius and S. Glagov. J Vasc Surg 7(3):386-394, 1988.
2) Aortic wall metabolism in relation to susceptibility and resistance to experimental atherosclerosis. P.J. Cozzi, R.T. Lyon, H.R. Davis, S. Glagov and C.K. Zarins. J Vasc Surg 7(5):706-714, 1988.
3) Hemodynamics and atherosclerosis: Insights and perspectives gained from studies of human arteries. S. Glagov, C.K. Zarins, D.P. Giddens, and D.N. Ku. Arch Path Lab Med 112(10):1018-1031, 1988.
4) Critical carotid stenoses: Morphologic and biochemical similarity of symptomatic and asymptomatic plaques. H.S. Bassiouny, H. Davis, N. Massawa, B.L. Gewertz, S. Glagov and C.K. Zarins. J Vasc Surg 9(2):202-212, 1989.

ZARINS P2

CONTINUATION PAGE FOR
BIOGRAPHICAL SKETCH

(Use additional pages if necessary to complete the following.)

NAME (Last, first, middle initial)
Zarins, Christopher K.

SOCIAL SECURITY NUMBER
125-34-3613

5) Flow patterns in the abdominal aorta under simulated postprandial and exercise conditions: An experimental study. D.N. Ku, S. Glagov, J.E. Moore, Jr. and C.K. Zarins. J Vasc Surg 9(2):309-316, 1989.
6) Atlas of vascular surgery. Christopehr K. Zarins and Bruce L. Gewertz. Churchill Livingstone, Inc., New York, New York, 1988.
7) The contribution of valves to saphenous vein graft resistance. D.N. Ku, J.M. Klafta B.L. Gewertz and C.K. Zarins. J Vasc Surg 6:274-279, 1987.
8) Compensatory enlargement of human atherosclerotic coronary arteries. S. Glagov, E. Weisenberg, G. Kolettis, R. Stankunavicius and C.K. Zarins. NEJM 316:1371-1375, 1987.
9) Vessel, plaque and lumen morphology after transluminal balloon angioplasty: A quantitative study in distended human arteries. R.T. Lyon, C.K. Zarins, C-T Lu, C-F Yang and S. Glagov. Arteriosclerosis 7(3):306-314, 1987.
10) Transesophageal echocardiographic monitoring of myocardial ischemia during vascular surgery. B.L. Gewertz, P.C. Kremser, C.K. Zarins, J.S. Smith, J.E. Ellis, S.B. Feinstein, and M.F. Roizen. J Vasc Surg 5:607-613, 1987.
11) Protection from atherosclerotic lesion formation by reduction of artery wall motion. R.T. Lyon, A. Runyon-Hass, H.R. Davis, S. Glagov, and C.K. Zarins. J Vasc Surg 5)1):59-67, 1987.
12) Shear stress regulation of artery lumen diameter in experimental atherogenesis. C.K. Zarins, M.A. Zatina, D.P. Giddens, D.N. Ku and S. Glagov. J Vasc Surg 5(3):413-420, 1987.
13) The effects of diabetes on the development of atherosclerosis. A.M. Graham and C.K. Zarins. Bruit 10:182-185, 1986.
14) Efficacy of isolated profundaplasty. A.M. Graham, B.L. Gewertz and C.K. Zarins. Can J Surg 29(5):330-332, 1986.
15) New criteria for prophylactic vena cava filter placement. J.J. Alexander, B.L. Gewertz, C-T Lu and C.K. Zarins. SG&O 163(5):405-409, 1986.
16) Predicting cerebral ischemia during carotid endarterectomy. A.M. Graham, B.L. Gewertz, and C.K. Zarins. Arch Surg 121:595-598, 1986.
17) Spectral analysis of EEG during carotid endarterectomy. L.V. Ivanovic, R.S. Rosenbe V.L. Towle, A.M. Graham, B.L. Gewertz, C.K. Zarins, and J-P Spire. Annals of Vasc S 1:112-117, 1986.
18) "Spontaneous" dissection of the extracranial vertebral arteries. L.R. Caplan, C.K. Zarins and M. Hemmati. Stroke 16(6):1030-1038, 1986.
19) Increased collagenase activity in early aneurysmal dilatation. C.K. Zarins, A. Runyon-Hass, M.A. Zatina, C-T Lu, and S. Glagov. J Vasc Surg 3:238-248, 1986.
20) Repair of vertebral artery dissection: case report. J.J. Alexander, S. Glagov, and C.K. Zarins. J Neurosurg 64:662-665, 1986.
21) Pulsatile flow and atherosclerosis in the human carotid bifurcation: positive correlation between plaque localization and low and oscillating shear stress. D.N. Ku, D.P. Giddens, C.K. Zarins and S. Glagov. Arteriosclerosis 5:293-302, 1985.
22) Plasma lipoprotein changes attending the intravenous administration of Triton WR-1339 in normolipidemic dogs: preferential effect on high density lipoproteins. C. Edelstein, R.E. Byrne, K. Yamamoto, C.K. Zarins and A.M. Scanu. J of Lipid Research 26:351-359, 1985.
23) Revascularization of the external carotid artery. C.K. Zarins. J Vasc Surg 2:232-234, 1985.
24) Role of acid lipase in cholesteryl ester accumulation during atherogenesis: correlation of enzyme activity with acid lipase-containing macrophages in rabbits and human lesions. H.R. Davis, S. Glagov and C.K. Zarins. Atherosclerosis 55: 205-215, 1985.

BIOGRAPHICAL SKETCH SCHEDULE C-1

Give the following information for the key personnel and consultants listed on page 2. Begin with the Principal Investigator/Program Director. Photocopy this page for each person.

NAME	POSITION TITLE	BIRTHDATE (Mo., Day, Yr.)
GLAGOV, Seymour	Professor, Depts. of Pathology and Medicine	8/8/25

EDUCATION (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
Brooklyn College, Brooklyn, New York	B.A.	1946	Physics
University of Geneva, Geneva, Switzerland	M.D.	1953	Medicine (Assistantship in Physiology)

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. DO NOT EXCEED TWO PAGES.

1954-58	Intern and Resident, Medicine and Pathology, Beth-El Hospital
1958-61	Instructor, Department of Pathology, University of Chicago
1958-60	Research Fellow, American Heart Association
1960-62	Advanced Research Fellow, American Heart Association
1961-66	Assistant Professor, Department of Pathology, University of Chicago
1962-67	Established Investigatorship, American Heart Association
1963-64	Visiting Research Associate, Nuffield Inst. for Med. Res. Oxford
1966-70	Associate Professor, Department of Pathology, University of Chicago
1970-Present	Professor of Pathology and Medicine, University of Chicago
1985-87	Chairman, Committee on Vascular Lesions, AHA

HONORS:

1971-75,81-87	Member Cardiovascular B Study Section, NIH
1978-80	AHA Pathology Study Section

REPRESENTATIVE PUBLICATIONS: (Last 2 years only)

Zarins, C.K., Glagov, S. and Giddens, D.P.: Adaptive enlargement of arteries in response to increased flow and increased intimal plaque. In "Role of Blood in Atherogenesis", Y. Yoshida, T. Yamaguchi, C.G. Caro, S. Glagov and R.M. Nerem (eds.). (Proc. Int's. Symposium on the Role of Blood Flow in Atherosclerosis. Hyogo, October, 1987) Springer-Verlag, New York, 1988, 185-188.

Cozzi, P.J., Lyon, R.T., Davis, H.R., Sylora, J., Glagov, S. and Zarins, C.K.: Aortic wall metabolism in relation to susceptibility and resistance to experimental atherosclerosis. J. Vasc. Surg., 7, 706-714, 1988.

Zarins, C.K., Weisenberg, E., Kolettis, G., Stankunavicius, R. and Glagov, S.: Differential enlargement of artery segments in response to enlarging atherosclerotic plaques. J. Vasc. Surg., 7, 386-394, 1988.

Zarins, C.K. and Glagov, S.: Artery Wall Pathology in Atherosclerosis. In Vascular Surgery, 3rd Edition. Rutherford, R.B. ed., W.B. Saunders, Philadelphia, 1989, pp 178-193

Taylor, K.E., Glagov, S. and Zarins, C.K.: Preservation and structural adaptation of endothelium over experimental foam cell lesions: A quantitative ultrastructural study. Arteriosclerosis, 9, 881-894, 1989.

Glagov, S., Newman, W. III, Schaffer, S. (eds.) Pathobiology of Human Atherosclerotic Plaque. New York, Springer-Verlag, 1989.

GLAGOV # 2

Glagov S. and Zarins, C.K.: Is intimal hyperplasia an adaptive response or a pathologic process? Observations on the nature of non-atherosclerotic intimal thickening. J. Vasc. Surg. in press (Oct or Nov 1989)

Giddens, D.P., Zarins, C.K., Ku, D.N. and Glagov, S.: The utility of correlations between model flow studies and vessel pathology in describing atherogenesis. In "Role of Blood Flow in Atherogenesis", Y. Yoshida, T. Yamaguchi, C.G. Caro, S. Glagov and R.M. Nerem (Eds.). (Proc. Int'l. Symposium on the Role of Blood in Atherogenesis, Hyogo, October, 1987), Springer-Verlag, New York, 1988, pp 65-66.

Ku, D.N., Zarins, C.K., Giddens, D.P. and Glagov, S.: Early atherosclerosis and pulsatile flow in the human carotid bifurcation. In "Role of Blood Flow in Atherogenesis", Y. Yoshida, T. Yamaguchi, C.G. Caro, S. Glagov and R.M. Nerem (Eds.). (Proc. Int'l. Symposium on the Role of Blood Flow in Atherogenesis. Hyogo, October, 1987), Springer-Verlag, New York, 1988, pp 73-80.

Ku, D.N., Glagov, S., Moore, J.E. and Zarins, C.K.: Flow patterns in the abdominal aorta under simulated postprandial and exercise conditions: An experimental study. J. Vasc. Surg., 9, 309-316, 1989.

Bassiouny, H.S., Davis, H., Masawa, N., Gewertz, B.L., Glagov, S. and Zarins, C.K.: Critical carotid stenosis: Morphological and chemical similarity between symptomatic and asymptomatic plaques. J. Vasc. Surg., 9, 202-212, 1989.

Glagov, S. and Zarins, C.K.: What are the determinants of plaque instability and its consequences. J. Vasc. Surg., February, 1989.

Zarins, C.K., Glagov, S., Giddens, D.P. and Ku, D.N.: Hemodynamic factors and atherosclerotic change in the aorta. In Aortic Surgery. Bergan J.J. and Yao, J.S.T. ed. W.B. Saunders, 1988, pp 17-25.

Glagov, S., Zarins, C.K., Giddens, D.P. and Ku, D.N.: Hemodynamics and Atherosclerosis: Insights and perspectives gained from studies of human arteries. Arch. Path. Lab. Med. 112, 1018-1031, 1988.

Bassiouny, H.S., Lieber, B.B., Zu, C.P., Giddens, D.P., Glagov, S. and Zarins, C.K.: Quantitative inverse correlation of wall shear stress with experimental intimal thickening. Surgical Forum, 39, 328-330, 1989.

Rich, S., Miller, J.F., Charous, S.J., Davis, H.R., Shanks, P., Glagov, S. and Lands, W.E.M.: The development of atherosclerosis in genetically hyperlipidemic rabbits during chronic fish oil ingestion. Arteriosclerosis 9, 189-194, 1989.

Zarins, C.K. and Glagov, S.: Histopathology of plaque dilatation and remodelling following balloon angioplasty. In Endovascular Surgery, W.S. Moore and S.S. Ahn (Eds.) W.B. Saunders, Philadelphia, pp 141-147.

Grande, J.P., Glagov, S., Bates, S.R., Horwitz, A.L. and Mathews, M.B.: Effect of normolipemic and hyperlipemic serum on the biosynthetic response to cyclic stretching of aortic smooth muscle cells. Arteriosclerosis, 9, 446-452, 1989.

Glagov, S., Bassiouny, H., Masawa, N., Ku, D.N., Vito, R.P., Giddens, D.P. and Zarins, C.K.: Hemodynamic and Structural Determinants of Human Plaque Stability. In Atherosclerosis VIII, Crepaldi, G., Gotto, A.M., Manzato, E. and Baggio, G. Excerpta Medica, Amsterdam, 1989, pp 411-415.

Glagov, S., Grande, J.P., Xu, C-p., Giddens, D.P. and Zarins, C.K.: Limited effects of hyperlipidemia on the arterial smooth muscle response to mechanical stress. J. Cardiovasc. Pharm. 14(Suppl.6): S90-S97, 1989.

VISUALIZATION OF FLOW PHENOMENA IN A VASCULAR GRAFT MODEL
A Thesis Presented to The Academic Faculty by Samuel Scott White, December 1989

SUMMARY

Vascular reconstructions are sometimes necessary to restore circulation in diseased arterial segments of the lower extremity. The region where a graft joins the native vessel is an *anastomosis*. Flow patterns, wall compliance and motion, and vessel geometry are altered at an anastomosis, and the intima of the native artery can adapt to these local changes. Fibrous proliferation of the intima into the anastomosis is known as *intimal hyperplasia*.

Only two thirds of bypasses performed in the lower extremity remain patent after two years. The major cause of failure in these small arterial (dia < 4mm) bypasses is intimal hyperplasia. Current evidence shows a positive correlation between intimal thickening and regions of low and oscillating wall shear stress in the human carotid arteries, it is hypothesized that such near wall conditions exist in the region of an anastomosis, and that these conditions lead to intimal hyperplasia and graft failure.

Canine experiments performed at The University of Chicago School of Medicine provided information for anastomotic geometries and flow waveforms. From these in vivo data, two

scaled end-to-side anastomosis models have been constructed. Only one geometric parameter, the ratio of anastomotic hood length to host artery diameter, was varied between the models. Model I had a ratio of 4:1 and model II had a ratio of 8:1. The models were placed in a flow system which was operated under steady and pulsatile flow conditions. The flow phenomena observed in the anastomoses were recorded on 35 mm black and white film and VHS video tape. The steady flow experiments were conducted at Reynolds numbers 1000, 650, and 200. The flow divisions between the proximal-distal exits were 0%-100%, 20%-80%, 50%-50%, and 100%-0%.

Laminar flow patterns were observed for steady flow in all configurations except the 100%-0% flow division at Reynolds numbers 650 and 1000. Secondary flow occurred around the anastomotic sinus in both models because a radial pressure gradient was induced by the slope in the anastomotic hood. Fluid did not separate from the hood in any case, but recirculation zones were present at the wall opposite the hood in both models for low proximal outflow.

The pulsatile experiments revealed that regions of low and oscillatory shear stress are present within an anastomosis along the opposite wall and near the distal exit. Low shear at the opposite wall occurred near the end of systole for both models. The pulsatile flow separated from the hood during

portions of the cycle in model I when the proximal outflow increased to 50%. In model II, flow separation from the hood was observed for all configurations.

A region of high particle residence time was also discovered. Particle accumulation in the anastomotic sinus began at the model inlet and extended to the outer wall for the 0%-100% flow division. As proximal outflow was increased to 20%, a C-shape was formed. A proximal outflow greater than 50% prevented particle accumulation.

The results from the flow visualization experiments suggest that the anastomotic regions suseptible to intimal hyperplasia are along the hood near the distal exit and along the wall of the native artery. Clinical observations confirm that hyperplasia does develop at these locations. Chronic animal studies currently being performed at The University of Chicago School of Medicine will provide in vivo data of intimal hyperplasia development in canine bypass grafts. At the completion of the chronic studies (6 months), a correlation will be made between the actual locations of hyperplasia in anastomoses with those predicted by the flow experiments.